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Valve-Incompetent Foramen Ovale in Premature Infants With Ductus Arteriosus: A Doppler Echocardiographic Study

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In a 1 year period, 56 neonates with a clinical diagnosis of ductus arteriosus had Doppler echocardiographic confirmation of the ductus; 33 (59%) had additional, turbulent left to right flow at the atrial level through a valve-incompetent foramen ovale. Normalized left atrial dimensions in the group with the atrial shunt were significantly larger than when there was a competent foramen ovale; when the ductus closed and left atrial enlargement receded, the atrial shunt disappeared. However, several infants with large left chambers had no interatrial shunting. When the atrial shunt was present, there were up to three flow pulses, corresponding to atrial systole, ventricular systole and ventricular diastole, but these were frequently fused into two pulses or even one pulse per cycle. The atrial septal morphology provided supporting clues: general bowing of the septum or a localized bulge in the region of the foramen ovale indicated relatively high left atrial pressure, and frequently a slitlike dropout could be seen at the superior edge of the foramen.

During the study, three additional neonates with a ductus arteriosus were found to have a secundum atrial septal defect with a typical echographic image, "matchhead" appearance of the septal rim of the defect, but the Doppler flow patterns were indistinguishable from those of a valve-incompetent foramen ovale. The hemodynamic effects of the interatrial shunt, from either cause, seemed slight during the hospital course, but the presence of a valve-incompetent foramen ovale indicated a relatively large ductal shunt. Quantification of the ductal shunt, however, continues to rely primarily on measurement of the left atrial and ventricular size.

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Interatrial left to right shunting due to incompetence of the foramen ovale secondary to dilation of the left atrium has been reported in a number of conditions such as mitral valve disease (1), severe left heart failure (2), ductus arteriosus (3,4) and ventricular septal defect (4). In these studies the diagnosis was made by cardiac catheterization and was confirmed by surgery or autopsy. Patent ductus arteriosus has been demonstrated to be a common complication in premature infants. The prevalence and clinical significance of associated valve-incompetent foramen ovale in infants with patent ductus arteriosus have not been systematically investigated. Doppler echocardiographic techniques allow safe, noninvasive diagnosis and serial evaluation of both ductus arteriosus and interatrial shunting (5–7). This study reports the prevalence of valve-incompetent foramen ovale, describes their Doppler waveforms and their hemodynamic implications and correlates the presence of shunts with changes in chamber size. In addition, the echocardiographic and Doppler characteristics of secundum atrial septal defects were compared with those of the valve-incompetent foramen ovale.

Methods

Study patients. Between January 1985 and January 1986, 56 consecutive neonates with the clinical diagnosis of ductus arteriosus from the nurseries of the University of Washington Hospital were studied echocardiographically for clinical indications; 36 were male and 20 were female. Among them, three were full term infants whereas the rest were premature infants whose weight ranged from 460 to 2,300 g (mean 996) at the first echographic study, carried out at a postnatal age of 1 to 25 days (mean 7.5). For individual patients, one to six (mean two) serial echocardiographic studies were performed within 6 months of birth. A total of 114 studies were obtained for retrospective analysis. The diagnosis of a ductus was established by Doppler echocardiographic examination; three patients had an additional small ventricular

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septal defect detected by Doppler interrogation but the defect could not be seen on real-time two-dimensional imaging. Three infants with a ductus were diagnosed as having a secundum atrial septal defect; these three are not included in the group statistics.

Echocardiography. An Advanced Technology Laboratory MK 600 Ultrasound System with a 7 MHz transducer was used. This transducer functions at 5 MHz for Doppler recording. All patients were examined in the supine position, and in many instances the infants were on a ventilator with sedation. Standard parasternal short-axis and suprasternal views were employed to confirm the patency of the ductus by recording disturbed flow signals toward the transducer when interrogating the pulmonary trunk or ductal lumen at the origin in the descending aorta (5).

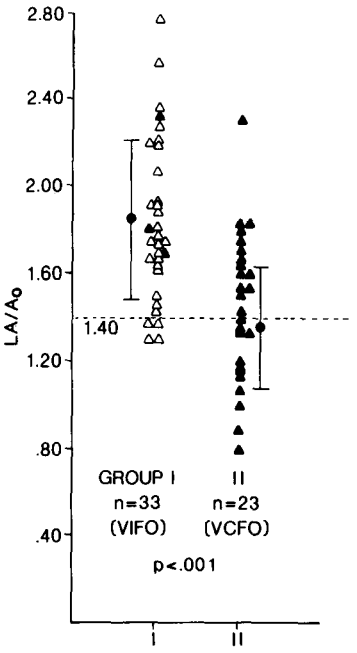
The morphologic features and displacement of the interatrial septum were analyzed for general or localized bowing toward the right atrium, flap motion at the foramen ovale and dropout of the septal echo in the region of the foramen. These morphologic features are conditions favorable for the diagnosis of a left to right shunt at the foramen ovale. This anatomy is usually best visualized from the subcostal approach, which is also the approach that provides the most nearly axial Doppler flow signal if a left to right shunt occurs at the foramen. The entire septum on the right atrial side is interrogated with the Doppler sample volume, but particular attention is given to any echo feature of local dropout or bulge. The audio signal with a valve-incompetent foramen ovale will reveal turbulent flow (hissing and harsh, as opposed to either a low frequency or whistling, musical sound). Deliberate identification of the superior vena cava flow is helpful to avoid mistaking that flow for that of a valve-incompetent foramen ovale; the caval flow is usually musical, but may become harsh and turbulent with inspiration, whereas there should be no respiratory pattern to interatrial flow. Vena caval flow during atrial systole will usually be negative (away from the right atrium) during atrial systole, but foramenal flow will be positive, or toward the right atrium. Tricuspid regurgitation produces turbulent systolic flow in the right atrium, and can be distinguished because it has a negative systolic flow pulse recorded by Doppler interrogation from the subcostal approach and is maximal at the valve. Low velocity, nonturbulent flow signals may be found throughout the right atrium, and should not be attributed to foramenal flow, which is localized, turbulent and of higher velocity.

Chamber dimensions. Guided by two-dimensional imaging and a cursor line, conventional M-mode echocardiography from the precordial long-axis plane was recorded on a strip chart. M-mode measurements were taken, using the leading edge principle and the peak of the R wave from the electrocardiogram (ECG) as reference for ventricular end-diastole. Left atrial (LA) dimensions were normalized by aortic (Ao) root dimension as the ratio LA/Ao, whereas end-diastolic dimensions of the left ventricle (LV) were normalized by mean values of the left ventricle for weight by the ratio $LV/\overline{LV}$; $\overline{LV}$ was taken from published data (8,9). All two-dimensional and Doppler studies were recorded on videotape and reviewed independently by each of us. *Statistical comparisons* were performed with Student's *t* test.

Results

Fifty-six neonates with ductus arteriosus diagnosed by Doppler echocardiography were followed up to discharge from the neonatal intensive care unit. Twelve infants died of complications of prematurity; 6 underwent autopsy and none had a secundum atrial defect or any congenital heart defect other than a ductus arteriosus. Three premature infants with a ductus arteriosus were diagnosed on echocardiography as having a secundum atrial septal defect, on the

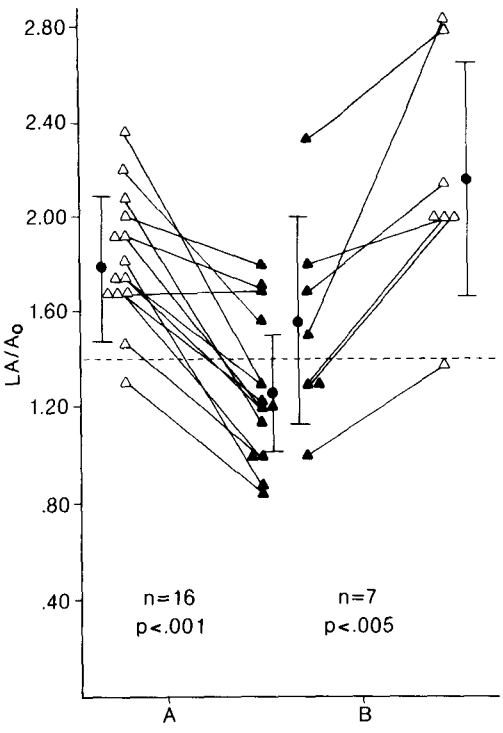
Figure 1. Initial studies of the left atrial/aortic root diameter (LA/Ao) ratio in two groups of infants with ductus arteriosus. Group I comprises 33 patients who have had a valve-incompetent foramen ovale (VIFO) at some time. Group II includes 23 infants with no interatrial shunt (valve-competent foramen ovale) (VCFO). The difference in ratios between the two groups is significant at the $p < 0.001$ level. The **dotted line** at 1.40 on the **ordinate** represents the ratio suggested as the threshold for hemodynamically significant ductus arteriosus (9); there are 4 of 33 patients in Group I with a ratio below that threshold. Note that approximately half the patients in Group II who have no atrial shunt have significant enlargement of the left atrium. **Solid triangles** indicate no atrial shunt, **open triangles** indicate interatrial shunting. The three **solid triangles** in Group I represent infants with a subsequent echocardiogram that indicated development of shunting. The **vertical bars** present the standard deviation around the mean.



basis of a persistent, relatively large dropout of the interatrial septal echo associated with left to right flow at that site. The rim of the defect was increased in thickness, producing a typical match-head appearance, lacking in the 56 infants diagnosed as having a valve-incompetent foramen ovale. One of these three died and the diagnosis of atrial septal defect was confirmed at autopsy; the two survivors still have echographic and Doppler evidence of an atrial septal defect more than 4 months after closure of their ductus.

Valve-incompetent foramen ovale and enlargement of the left atrium and ventricle. Fifty-six infants with a ductus arteriosus confirmed by Doppler echocardiography, and with no atrial septal defect, were examined for a left to right shunt at the atrial level; 33 patients (59%) had at least one positive echocardiogram (Group I). In this group there were a total of 79 studies. In the other 23 patients (Group II), there were 35 studies; no atrial shunt was identified on single or serial examinations. The association between an atrial shunt and enlarged left atrial dimension is demonstrated by the mean values for normalized left atrial size from Groups I and II, based on the initial studies (Fig. 1). Group I infants with an atrial shunt had a mean left atrial/aortic root ratio of 1.85 ± 0.37 (mean ± SD). Group II infants with no atrial shunt had a mean ratio of 1.36 ± 0.27, a difference

Figure 2. Paired studies of 23 individual patients in Group I, comparing left atrial/aortic root (LA/Ao) ratios with and without interatrial shunting. **A,** The shunt was present initially and then disappeared; **B,** the shunt developed. The differences for both **A** and **B** sets of patients are significant ($p < 0.001$ and 0.005, respectively).



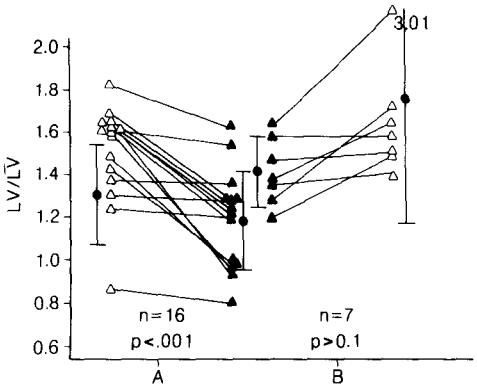


Figure 3. Paired studies of the same 23 patients as in Figure 2, comparing normalized left ventricular dimensions according to mean predicted for weight ($LV/\overline{LV}$), when the interatrial shunt disappeared **(A)** or appeared **(B)**.

significant at the 0.001 level. Nevertheless, approximately half of the Group II infants with no atrial shunt had significant enlargement of the left atrium.

In individual patients who had more than one ultrasound examination, the presence of an atrial shunt continued to correlate with the normalized left atrial size (Fig. 2). Sixteen infants who initially had an atrial shunt had an average left atrial/aortic root ratio of 1.77 ± 0.31; subsequently, when the same patients had no atrial shunt, the ratio was 1.25 ± 0.25 ($p < 0.001$). Seven infants who initially had no atrial shunt and who had a mean left atrial/aortic root ratio of 1.56 ± 0.43 subsequently developed an atrial shunt and had an increased mean ratio of 2.17 ± 0.51 ($p < 0.005$).

Changes in left ventricular end-diastolic dimension were also associated with the presence of an atrial shunt. Figure 3 reveals a significant decrease in normalized left ventricular size ($LV/\overline{LV}$) after disappearance of the atrial shunt in 26 infants, from 1.50 ± 0.23 to 1.18 ± 0.23 ($p < 0.001$). Of the seven infants who initially had no atrial shunt and developed one later, the mean normalized left ventricular size increased from 1.41 ± 0.16 to 1.77 ± 0.56, but the difference was not significant ($p > 0.1$).

Doppler flow patterns of interatrial left to right shunt. With the Doppler sample volume placed perpendicularly to the atrial septum from the subcostal window, a prominent Doppler flow signal could be detected at the foramen ovale in Group I patients, with a variety of waveforms seen in spectral display (Fig. 4). The Doppler waveforms were essentially the same as described in Doppler echocardiographic studies of atrial septal defects (7,10,11). There were one to three positive (toward the transducer) flow peaks, and the relative velocity for each varied from patient to patient, and the degree of fusion of the three also varied. Atrial systole produced a small, usually positive flow (unlike caval flow, which is reversed at that time) (Fig. 5). The two major flow pulses through the valve-incompetent for-

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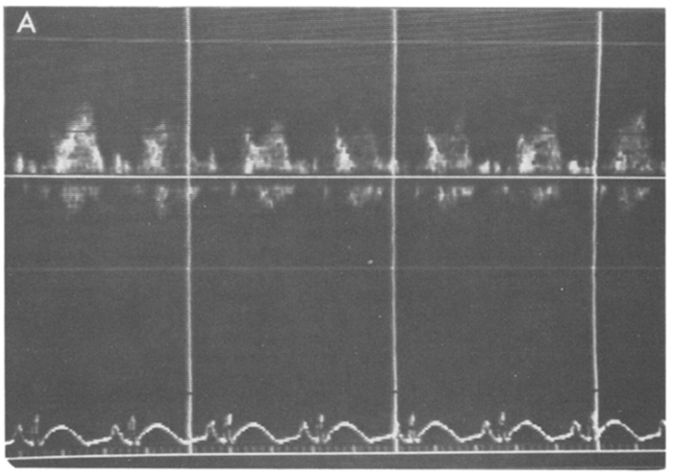

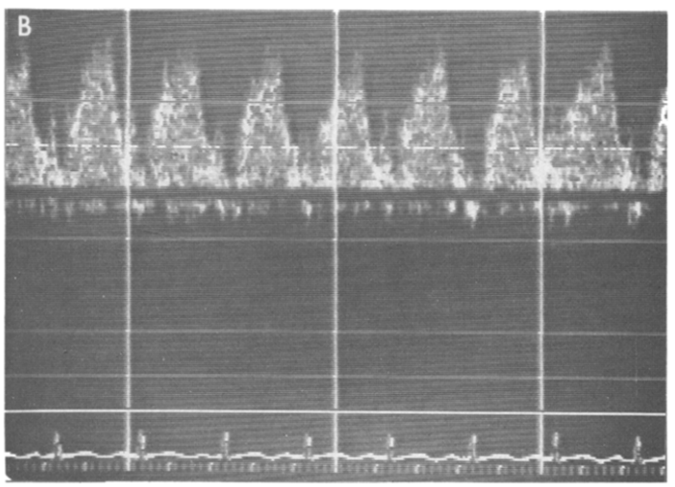

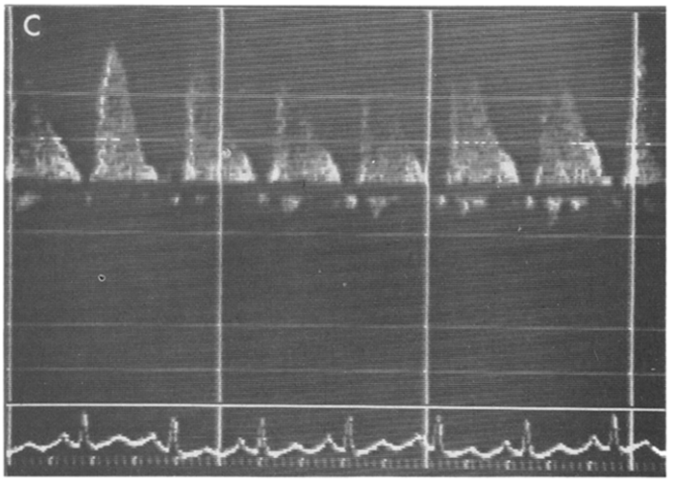

Figure 4. Three characteristic flow patterns recorded by Doppler ultrasound (5 MHz) at the foramen ovale in infants with a valve-incompetent foramen and ductus arteriosus; the ECG is recorded **below.** In each case, the flow is predominantly toward the transducer and therefore above the zero-flow line. **A,** The central five beats reveal a small pulse with atrial systole, and two larger pulses of nearly equal amplitude during ventricular systole and diastole. The first and last cycles show only two distinct pulses, with fusion of the two ventricular pulses. **B,** A brief but significant atrial systolic pulse and a single large flow peaking in early diastole. **C,** Some atrial pulses are reversed; the ventricular systolic flow pulse is dominant, resembling a vena caval flow pattern.

amen ovale are coincident with ventricular systole and diastole. Distinct, separate pulses were observed in 23 of 52 studies with interatrial shunting in Group I. These pulses were fused to provide only one pulse per cycle in 29 of the 52.

In all the studies of Group II patients, Doppler interrogation along the right side of the atrial septum showed nothing but low velocity (usually <0.2 to 0.3 m/s) and nonturbulent flow signals; except in some instances, the velocity of those signals intermittently became high during the respiratory cycle, but maintained laminar flow, suggesting vena caval flow. The same findings were observable in Group I patients when the atrial shunt no longer existed.

The Doppler flow patterns for the three patients with a secundum atrial septal defect were indistinguishable from the patterns in patients with a valve-incompetent foramen ovale.

Morphology of the atrial septum. From the subcostal four-chamber plane, the interatrial septum was clearly seen in every patient. Several morphologic phenomena were of special interest (Fig. 6). First, general bowing of the septum toward the right atrium, defined as a deflection >1 mm from the baseline, occurred in the majority of patients with a ductus arteriosus. Second, a localized septal bulge toward the right may or may not combine with general bowing. The extent of displacement of this local feature varied in different phases of the cardiac cycle, with the maximal excursion in late systole, coinciding with peaking of the Doppler-documented left to right shunt. Both these phenomena, generalized and local displacement of the interatrial septum, were common with or without atrial shunting, and are thought to reflect elevated left atrial pressure. Only 12 infants were completely free of bowing or bulging of the septum.

Frequently, opening of the flap of the foramen ovale could be seen as an echo dropout, particularly at the cephalad end of local bulge. It usually was a slitlike but constant discontinuity of the septum, never exceeding 0.3 cm in our series and never having the match-head appearance of the septal rim of the defect characteristic of a secundum atrial defect. Atrial septal echo dropout without septal bowing or bulging was uncommon. A brief, abrupt displacement of the middle to lower part of the atrial septum with each cardiac cycle was observed in 14 studies of 12 infants. The segment of the septum moved quickly toward the left atrium at the end of diastole, then abruptly swung back to the midline and remained there for the rest of the cycle. When

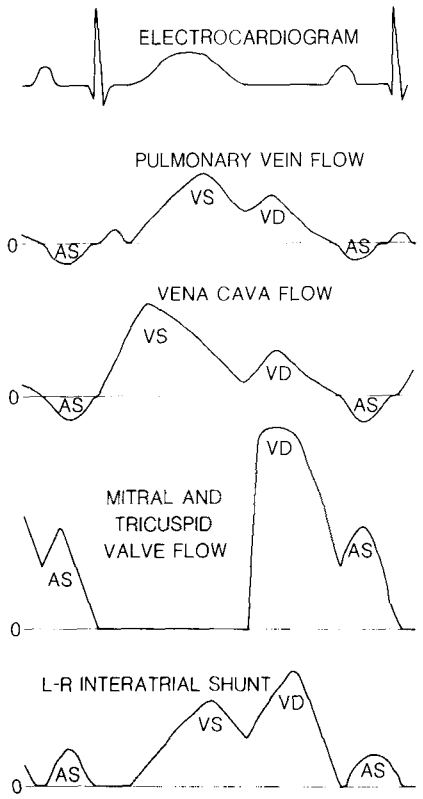

Figure 5. Hemodynamic events influencing the flow patterns in interatrial shunting. The flows in the pulmonary vein and vena cava are taken from studies in dogs with implanted pulsed ultrasound flowmeters (13–15). Flows across the mitral and tricuspid valves are typical patterns in human subjects using the Doppler technique. The interatrial flow is characteristic of infants with valve-incompetent foramen ovale or actual atrial septal defect. The patterns vary, representing varying contributions from the input and output of the two atria. AS = atrial systole; L-R = left to right; VD = ventricular diastole; VS = ventricular systole.

this type of displacement occurred, no atrial shunt was found, with a single exception.

Discussion

Doppler diagnosis of interatrial shunting. Duplex Doppler ultrasound has been demonstrated to be a reliable tool for noninvasive diagnosis of interatrial shunts. In the case of atrial septal defect, sensitivity and specificity of 93 and 94%, respectively, have been achieved (12). In 18 of our 56 patients, we observed the appearance, disappearance and even reappearance of an interatrial shunt, consistently accompanied by changes in left atrial size. Doppler echocardiography is particularly convenient to follow patients, so that the elimination of shunt flow at the atrial level after the removal of its cause, that is, ductal shunt and associated left atrial enlargement, can be easily documented. This disappearance of the atrial shunt constitutes a useful diagnostic criterion to distinguish a valve-incompetent foramen ovale from a secundum atrial septal defect, in addition to the echographic findings of a rim around the latter defect (Table 1).

Figure 6. Three typical two-dimensional echocardiographic changes related to interatrial shunting. On the **top row** are line drawings of the freeze-frames **(bottom row),** all from the subcostal window. **A,** Generalized bowing of the atrial septum toward the right atrium (RA), indicating increased left atrial (LA) pressure and volume. **B,** Localized bulge into the right atrium in the region of the foramen ovale, with small echo dropout at the superior margin of the bulge. **C,** Successive still frames indicating very brief and abrupt displacement of the interatrial septum. This pattern indicates relatively balanced forces on both sides of the septum and was rarely associated with an interatrial shunt.

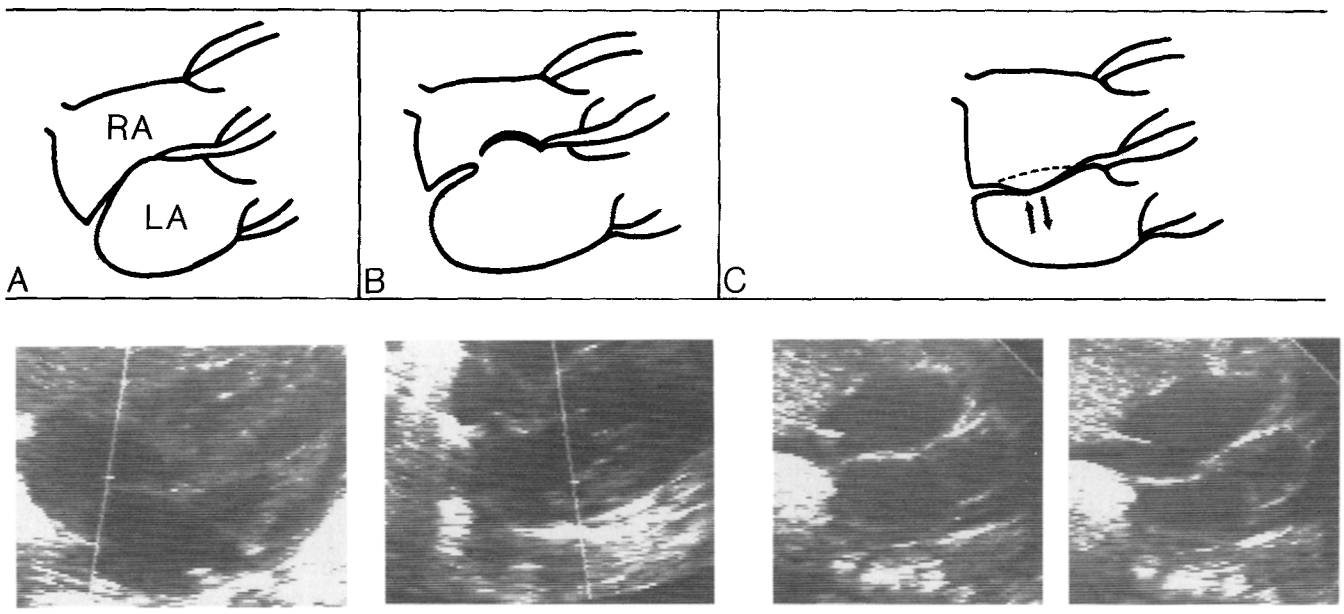

Table 1. Comparison of Valve-Incompetent Foramen Ovale and Secundum Atrial Septal Defect in Neonates

Valve-Incompetent Foramen Ovale	Secundum Atrial Septal Defect
1. Turbulent left to right flow, reflecting a significant pressure gradient between left and right atrium, and a small orifice; one to three flow pulses.	1. Flow turbulence varying inversely with size of defect. One to three flow pulses.
2. Orifice difficult to image, at cranial end of foramen ovale, usually slitlike; no "match-head" pattern of rim thickening.	2. Generally larger area of image dropout, more constant and seen from more than one plane; thickened rims, producing "match-head" pattern.
3. Interatrial septum usually bowed toward right atrium, with additional local bulge of the foramenal flap.	3. No displacement of septum except for small defects associated with a large left atrium.
4. Presence and persistence paralleling left atrial enlargement; disappearance when ductus closes.	4. Presence independent of left atrial size, and ductal shunt, if any.
5. Left atrial and ventricular enlargement without significant enlargement of right atrium and ventricle.	5. Enlargement of right atrium and ventricle, although mild in neonate.

Doppler flow patterns in valve-incompetent foramen ovale. The Doppler flow patterns we observed in infants with valve-incompetent foramen ovale and atrial septal defect varied from one to three left to right pulses. Kalmanson et al. (10) reported three distinct pulses in the atrial septal defect flow coincident with atrial systole, ventricular systole and early ventricular diastole. This pattern was found in 23 of our 52 studies (Fig. 4A). The other Doppler studies in secundum atrial septal defect (7,11) reported only two pulses, a small pulse with atrial systole and a major one that began in systole, but peaked at end-systole or early diastole, as seen in our Figure 4B. We observed this pattern in 29 of 52 studies, although in some the two waves merged to create a monophasic cycle. Included in these 29 studies were patterns with a dominant peak in early systole (Fig. 4C). From consideration of the inflow and outflow of the right and left atrium, namely the pulmonary veins (13) and the vena cavae (14,15) and the respective atrioventricular (AV) valves (Fig. 5), the flow across the interatrial septum must reflect those pulsatile events, but the relative magnitude of the pulses and the degree of fusion vary from one patient to another, and even in the same patient (Fig. 4A).

Morphology of interatrial septum. Although the Doppler demonstration of turbulent left to right shunt through the interatrial septum is the definitive criterion for diagnosis of either a valve-incompetent foramen ovale or a secundum atrial defect, the morphology of the interatrial septum aids in distinguishing the two causes of shunting. Dynamics of the atrial septum offer corroborative information, in addition to corroborative enlargement of the left atrium and ventricle. General bowing of the septum toward the right or a localized bulge to the right occurred in 52 of 79 studies in the presence of a left to right shunt by Doppler study (Group I). The visualization of an opening in the flap of the foramen ovale without a match-head rim was helpful in the rapid localization of the shunt, but was definite in only 12 of the 79 studies in Group I. An abrupt, brief displacement of the septum toward the *left* in late diastole predicted no atrial shunting.

Valve-incompetent foramen ovale in ductus arteriosus. The foramen ovale is normally patent at birth because its function in fetal life is to bypass the pulmonary circulation before the initiation of respiration by delivering much of the caval return to the left side of the heart. After respiration commences, the increased pulmonary venous return increases the left atrial pressure sufficiently to force the flap of the foramen ovale (septum primum) against the septum secundum. When the ductus arteriosus remains open, the left atrium enlarges in proportion to the size of the ductal shunt; the dilation may stretch the foramen ovale to the point that the valve or flap no longer covers the foramen in some infants. Because the pressure is now higher in the left atrium, a left to right shunt will occur with valve incompetence. We observed a 59% prevalence of valve-incompetent foramen ovale in infants with a ductus arteriosus, predominantly in those with significant enlargement of the left atrium. However, there were some patients with a large left atrium who had no interatrial shunt, indicating a variability in foramenal competence beyond simple left atrial enlargement. Incompetence of the foramen ovale depends on both the size of the flap and the size of the foramen. At autopsy, 20% of fetuses and newborn infants have a gap between the superior edge of the flap and the rim of the foramen (16). The presence of bowing of the septum in those cases could contribute to incompetence because bowing would increase the length of the arc, relative to a straight wall, and a formerly competent valve could become incompetent. Nevertheless, the presence of an interatrial shunt

indicated the presence of a large ductal flow with significant left atrial enlargement in the great majority of infants in our series. Further, when the shunt appeared or disappeared, the normalized left atrial size increased or decreased (Fig. 2), indicating a parallel between ductal shunting and interatrial shunting.

Hemodynamic significance. The hemodynamic significance of the interatrial shunt may be examined with respect to both the pulmonary and the systemic circulation. Although there are no adequate, precise data on normal right atrial and right ventricular dimensions, we observed no instances of substantial enlargement of these chambers in infants with valve-incompetent foramen ovale, suggesting that the increase in pulmonary flow with the atrial shunt was relatively slight. This is consistent with the relatively small interatrial shunting that occurs in the infant with an atrial septal defect, considering the limited compliance of the right ventricle in early infancy and the elevated pulmonary vascular resistance in premature infants with respiratory distress syndrome. Larger shunts might be expected in older, full term infants or children (1,2).

The effect of a valve-incompetent foramen ovale on the systemic circulation was considered by Rudolph et al. (3), who observed that their patients with an atrial shunt were among those who had the most severe symptoms; they speculated that the shunt might decompress the left atrium, preventing the development of adequate left ventricular filling pressure, and therefore reduce left ventricular output. (Actually, the drop in left atrial pressure could alleviate the pulmonary venous congestion and improve the patient's pulmonary compliance.) If left ventricular size is an indication of left ventricular filling, the positive association we found between the presence of an interatrial shunt and left ventricular size (Fig. 3) suggests that the valve-incompetent foramen ovale does not seriously reduce left ventricular filling.

Conclusion. The hemodynamic consequences of a valve-incompetent foramen ovale are minor in premature infants with a ductus arteriosus, and the presence of an interatrial shunt serves primarily as a marker of a significant ductal shunt. For quantification of the ductal shunt, we continue to rely primarily on left atrial and ventricular size, in the absence of depressed left ventricular systolic function.

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